Refine Search

Search Results -

Terms	Documents
L6 and 424/$.ccls.	112

Database:
US Pre-Grant Publication Full-Text Database
US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L7

Refine Search

Recall Text

Clear

Interrupt

Search History

DATE: Friday, June 08, 2007 **Purge Queries** Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L7	L6 and 424/$.ccls.	112	L7
L6	L5 and (polyvinyl adj1 pyrrolidone)	185	L6
L5	L4 and (polyvinyl adj1 acetate)	2064	L5
L4	L3 and (polyvinyl adj1 alcohol)	4198	L4
L3	(polyvinyl) same (phospholipid or lecithin)	8073	L3
L2	amisol	90	L2
L1	amisol$	136	L1

END OF SEARCH HISTORY

First Hit Previous Doc Next Doc Go to Doc#

Generate Collection Print

L19: Entry 21 of 82 File: PGPB Jul 1, 2004

DOCUMENT-IDENTIFIER: US 20040126419 A1
TITLE: Artificial tear formulation

Current US Classification, US Primary Class/Subclass:
424/450

Current US Classification, US Secondary Class/Subclass:
424/145.1

Summary of Invention Paragraph:
[0002] Present formulations of artificial tears act by replacing the volume of the tear film, but they can only do this while they remain in contact with the surface of the eye. A simple saline solution would remain in contact with the eye surface for only a few seconds and thus a viscosity improving component is required in the formulation. Such components presently used include hypromellose, hydroxyethylcellulose, carboxymethylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, dextran, hyaluronic acid, or carbomer 940 (polyacrylic acid). Such compounds act by mimicking the mucus present on the corneal surface and may interact with such mucus already present.

Summary of Invention Paragraph:
[0009] Thus the invention provides in one aspect, a formulation suitable for application to mammalian eyes, which formulation comprises a pharmaceutically acceptable, substantially isotonic aqueous electrolyte buffered at a pH of 5 to 8.5, containing a lipid binding protein such as tear lipocalin at a concentration of from 0.01 to 50 mg/ml, and a polar lipid selected from phospholipids and glycolipids, at a concentration of from 1 .mu.g/ml to 10 mg/ml.

CLAIMS:

1. A formulation suitable for application to mammalian eyes which formulation comprises: a pharmaceutically acceptable, substantially isotonic aqueous electrolyte buffered at a pH of 5 to 8.5, containing a lipid binding protein such as tear-specific prealbumin at a concentration of from 0.01 to 50 mg/ml; and a polar lipid selected from phospholipids and glycolipids, at a concentration of from 1 .mu.g/ml to 10 mg/ml.

Previous Doc Next Doc Go to Doc#

L19: Entry 25 of 82 File: PGPB Dec 18, 2003

DOCUMENT-IDENTIFIER: US 20030232089 A1
TITLE: Ophthalmic formulation with novel gum composition

Current US Classification, US Primary Class/Subclass:
424/488

Summary of Invention Paragraph:
[0004] Several different approaches have been attempted in order to overcome the disadvantages of solution-based eye-drops, outlined above. Specifically, various ophthalmic delivery systems, such as hydrogels, micro-and nanoparticles, liposomes, and inserts have all been investigated. Most of the formulation efforts have been aimed at maximizing ocular drug absorption through prolongation of the drug residence time in the cornea and conjunctival sac. Control of residence time has been accomplished to a minimal extent through the use of viscosifying agents added to aqueous solution, and to a greater extent, through the use of diffusion-controlled, non-erodible polymeric inserts (e.g. Ocusert.RTM., a trademark of Alza Corp.) This last solution has not been very successful because of a low degree of patient compliance, due to irritation, difficulty in insertion, and over-extended retention.

Summary of Invention Paragraph:
[0005] Viscosified solutions or gels have been accepted to a greater degree by patients, among other things, because of the ease of administration, lack of irritation of the eye as a result of administration thereto, and lower cost compared to other treatment methods. However, existing formulations of viscosified solutions only increase residence time of a drug in the eye to a limited extent, so the same solution must be applied to an eye multiple times to treat or prevent a given illness or infection of the eye. Many of the marketed ophthalmic formulations currently use the polymers hydroxypropyl methylcellulose, hydroxyethyl cellulose, and polyvinyl alcohol to increase the viscosity of the formulation. Other viscosity enhancers disclosed as being suitable for use in ophthalmic formulations include, but are not limited to propylene glycol alginate (U.S. Pat. No. 4,844,902; U.S. Pat. No. 5,776,445), tragacanth (U.S. Pat. No. 5,369,095).

Summary of Invention Paragraph:
[0025] The term "gum", as used herein, refers to any synthetic polymer, natural polysaccharide, or derivatized natural polysaccharide that is ophthalmically compatible and that increases the viscosity of a solution sufficiently to increase the viscosity of the solution in which it is found or to transform a drop of the solution into a semi-solid or gelatinous state after administration to an eye of a warm-blooded mammal. Examples of synthetic polymer gums include, but are not limited to, polyethylene glycol, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol and derivatives thereof, and Carbopol and derivatives thereof. Examples of natural polysaccharide gums include, but are not limited to, carrageenan, konjac, sodium alginate, aloe vera gel, agarose, guar, pectin, tragacanth, acacia, Arabic, curdlan, gellan, xanthan, scleroglucan, hyaluronic acid, or chitosan. Examples of derivatized natural polysaccharide gums include, but are not limited to, propyleneglycol alginate and hydroxypropyl guar.

Detail Description Paragraph:

[0059] In a preferred embodiment, the composition of the present invention as described above is used for amelioration of dry eye symptoms. When the composition is to be used for the amelioration of dry eye symptoms, it preferably further includes at least one additional component selected from the group consisting of polyvinyl alcohol, methyl cellulose, hydroxypropyl cellulose. The composition preferably further includes at least one agent that improves ocular tolerance, such as aloe vera gel, a buffering agent, and a tonicity modifier. The composition optionally includes an antimicrobial agent and/or a preservative.

Previous Doc Next Doc Go to Doc#

L19: Entry 55 of 82 File: USPT May 20, 2003

DOCUMENT-IDENTIFIER: US 6565861 B1
** See image for Certificate of Correction **
TITLE: Artificial tear formulation

Brief Summary Text (3):
Present formulations of artificial tears act by replacing the volume of the tear film, but they can only do this while they remain in contact with the surface of the eye. A simple saline solution would remain in contact with the eye surface for only a few seconds and thus a viscosity improving component is required in the formulation. Such components presently used include hypromellose, hydroxyethylcellulose, carboxymethylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, dextran, hyaluronic acid, or carbomer 940 (polyacrylic acid). Such compounds act by mimicking the mucus present on the corneal surface and may interact with such mucus already present.

Brief Summary Text (11):
Thus the invention provides in one aspect, a formulation suitable for application to mammalian eyes, which formulation comprises a pharmaceutically acceptable, substantially isotonic aqueous electrolyte buffered at a pH of 5 to 8.5, containing a lipid binding protein such as tear lipocalin at a concentration of from 0.01 to 50 mg/ml, and a polar lipid selected from phospholipids and glycolipids, at a concentration of from 1 .mu.g/ml to 10 mg/ml.

Current US Original Classification (1):
424/400

Current US Cross Reference Classification (1):
424/401

Current US Cross Reference Classification (2):
424/489

Current US Cross Reference Classification (3):
424/490

CLAIMS:

1. A formulation suitable for application to mammalian eyes which formulation comprises: a pharmaceutically acceptable, substantially isotonic aqueous electrolyte buffered it a pH of 5 to 8.5, containing a lipid binding protein at a concentration of from 0.01 to 50 mg/mL; and a polar lipid selected from phospholipids and glycolipids, at a concentration of from 1 .mu.g/ml to 10 .mu.g/ml, wherein the lipid and lipid binding protein are present as 4 soluble complex in the aqueous electrolyte.

14. A formulation suitable for application to mammalian eyes which formulation comprises: pharmaceutically acceptable, substantially isotonic aqueous electrolyte buffered at a pH of 5 to 8.5, containing a tear-specific prealburnin at a concentration of from 0.01 to 50 mg/mL; and a polar lipid selected from phospholipids and glycolipids, at a concentration of from 1 .mu./ml to 10 .mu.g/ml.

Previous Doc Next Doc Go to Doc#

L19: Entry 69 of 82 File: USPT Oct 17, 2000

DOCUMENT-IDENTIFIER: US 6132751 A
TITLE: O/W emulsion composition for eye drops

Abstract Text (1):
An O/W emulsion composition for eye drops comprises a drug selected from the group consisting of fluorometholone, clobetasone butyrate and clobetasol propionate; a phospholipid; liquid paraffine; and water. The O/W emulsion composition is excellent in solubility of fluorometholone, clobetasone butyrate and clobetasol propionate in the tear fluid. Therefore, the composition would exhibit an anti-inflammatory activity identical to or superior to those achieved by the conventional pharmaceutical preparations, by the administration thereof at a dose lower than those for these known drugs. The composition would also be excellent from the economical standpoint and permit reduction of systemic side effects which would be encountered when the conventional drugs are instilled in the eyes.

Brief Summary Text (2):
The present invention relates to an O/W emulsion composition for eye drops. More specifically, the present invention relates to an O/W emulsion composition for eye drops which comprises a drug selected from the group consisting of fluorometholone, clobetasone butyrate and clobetasol propionate, a phospholipid, liquid paraffin and water and which is excellent in solubility of fluorometholone, clobetasone butyrate and clobetasol propionate in the tear fluid.

Brief Summary Text (7):
On the other hand, there have been disclosed O/W emulsion compositions each of which comprises a drug, an oil, a phospholipid and a surfactant (J. P. KOKAI No. Hei 5-186333 and WO 94/05298) as prior arts concerning vehicles for instilled drugs hardly soluble in water in the eyes.

Brief Summary Text (9):
The present invention has been developed for solving the problems associated with the conventional techniques for solubilizing, in water, drugs hardly soluble in water and therefore, an object of the present invention is to provide a novel composition for eye drops which is excellent in solubility of fluorometholone, clobetasone butyrate and clobetasol propionate in the tear fluid. The inventors of this invention have conducted intensive studies to accomplish the foregoing object, have found out that an O/W emulsion composition which comprises one drug selected from the group consisting of fluorometholone, clobetasone butyrate and clobetasol propionate, a phospholipid, liquid paraffin and water permits the considerable improvement in solubility of fluorometholone, clobetasone butyrate and clobetasol propionate in the tear fluid and thus have completed the present invention.

Brief Summary Text (10):
More specifically, the present invention relates to an O/W emulsion composition which comprises one drug selected from the group consisting of fluorometholone, clobetasone butyrate and clobetasol propionate, a phospholipid, liquid paraffin and water. In the composition of the present invention, solubility of fluorometholone, clobetasone butyrate and clobetasol propionate in the tear fluid can be controlled by appropriately adjusting the mixing ratio of the components of the composition. The fluorometholone, clobetasone butyrate or clobetasol propionate-containing O/W

emulsion composition according to the present invention can effectively be used, in the form of an eye drop, for the treatments of various ocular diseases, for instance, inflammatory diseases of external- and anterior-ocular sites such as blepharitis, conjunctivitis, keratitis, scleritis, episcleritis, iritis, iridocyclitis and uveitis as well as inflammatory diseases developed after ocular operations.

Detailed Description Text (37):
The amount of liquid paraffin when incorporating FLM as the drug into the emulsion preferably ranges from 0.5 to 20 parts by weight, more preferably 3 to 20 parts by weight and most preferably 4 to 15 parts by weight per one part by weight of the phospholipid, and the concentration of liquid paraffin in the emulsion is preferably not more than 25% (w/v). If the liquid paraffin is used in an amount of not less than 0.5 part by weight per one part by weight of the phospholipid and when incorporating FLM into the emulsion, an emulsion can be prepared, which may ensure a particularly high concentration of FLM dissolved in the tear fluid. If the amount of the liquid paraffin to be used upon incorporation of FLM is less than 0.5 part by weight per one part by weight of the phospholipid, the phospholipid present in the emulsion is susceptible to oxidation and the resulting emulsion is insufficient in stability. On the other hand, if the amount of the liquid paraffin to be used upon incorporation of FLM is more than 20 parts by weight per one part by weight of the phospholipid, the emulsion system is liable to be easily destroyed and thus the system is quite unstable. Moreover, if the liquid paraffin concentration in the emulsion is not less than 25%, the resulting emulsion is in a cream-like state and this impairs the feeling when the emulsion is dropped in the eyes.

Detailed Description Text (39):
susceptible to oxidation and the resulting emulsion is insufficient in stability, while if the amount of the liquid paraffin to be used upon incorporation of CB is more than 80 parts by weight per one part by weight of the phospholipid, the emulsion system is liable to be easily destroyed and accordingly, the system is quite unstable. Moreover, if the liquid paraffin concentration in the emulsion is not less than 25%, the resulting emulsion is in a cream-like state and this impairs the feeling when the emulsion is dropped in the eyes.

Detailed Description Text (40):
The amount of liquid paraffin when incorporating CP as the drug into the emulsion preferably ranges from 0.5 to 80 parts by weight and more preferably 10 to 80 parts by weight per one part by weight of the phospholipid, and the concentration of liquid paraffin in the emulsion is preferably not more than 25% (w/v). If the liquid paraffin is used in an amount of not less than 10 parts by weight per one part by weight of the phospholipid and when incorporating CP into the emulsion, an emulsion can be prepared, which may ensure a particularly high concentration of CP dissolved in the tear fluid. If the amount of the liquid paraffin to be used upon incorporation of CP is less than 0.5 part by weight per one part by weight of the phospholipid, the phospholipid present in the emulsion is susceptible to oxidation and the resulting emulsion is insufficient in stability, while if the amount of the liquid paraffin to be used upon incorporation of CP is more than 80 parts by weight per one part by weight of the phospholipid, the emulsion system is liable to be easily destroyed and accordingly, the system is quite unstable. Moreover, if the liquid paraffin concentration in the emulsion is not less than 25%, the resulting emulsion is in a cream-like state and this impairs the feeling when the emulsion is dropped in the eyes.

Detailed Description Text (41):
When preparing the emulsion of the present invention, there may be added, to the essential component of the present invention, i.e., water, liquid paraffin or a phospholipid, sugars such as xylitol, mannitol and glucose; isotonizing agent such as propylene glycol and glycerol; pH adjusting agents such as sodium hydroxide and

hydrochloric acid; preservatives such as chlorobutanol, and parabens such as methyl p-hydroxybenzoate and propyl p-hydroxybenzoate; and/or thickeners such as methyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, propylene glycol, diethylene glycol and sodium polyacrylate, insofar as they do not impair the effect of the present invention.

Detailed Description Text (50):
Then the method for preparing the emulsion of the present invention will be explained below. A variety of known methods may be employed and, for instance, the emulsion of the present invention may be prepared by dissolving, with stirring, phospholipids such as yolk lecithin and, if desired, phosphatidylethanolamine and emulsifying adjuvants such as oleic acid, and a drug selected from FLM, CB and CP in an appropriate organic solvent such as hexane or ethanol, followed by distilling off the solvent under reduced pressure to thus form a thin film of the lipid. To the resulting thin film, there are added liquid paraffin and water and then the mixture is vigorously shaken and stirred to carry out pre-emulsification. The resulting liquid is emulsified in an emulsifier commonly used. To the liquid obtained after the emulsification, there may be added, for instance, a preservative and a stabilizer, followed by adjusting the pH value thereof to a desired level using HCl or NaOH to thus give an FLM, CB or CP-containing O/W emulsion according to the present invention. Further, the resulting emulsion is filled in an eye drop bottle, followed by sterilization to give an eye drop according to the present invention.

Detailed Description Text (108):
To a 2% aqueous glycerol solution (pH 8.0) containing 0.052% (w/v) methyl p-hydroxybenzoate, 0.028% (w/v) propyl p-hydroxybenzoate, 0.1% (w/v) polyvinyl alcohol (degree of polymerization 2000, available from Wako Pure Chemical Co., Ltd.), 0.1% (w/v) histidine and 0.04% (w/v) sodium citrate, there was added an equal volume of the CB emulsion according to the formulation 100 followed by sufficient mixing. After adjusting the pH of this mixture to 8.0 with NaOH, it was filtered through a membrane having a pore size of 0.8 .mu.m to thus prepare a CB emulsion containing the foregoing additives. The resulting emulsion was filled in an eye drop bottle, then thermally sterilized according to the fractional sterilization method to thus give an eye drop of the present invention. Moreover, the resulting eye drop of the present invention and Ageless (registered trademark) Z (available from Mitsubishi Gas Chemical Co., Inc.) were packaged together in a laminate bag of a polyethylene film and an aluminum foil according to the pillow-packaging technique.

Detailed Description Text (110):
To a 2% aqueous glycerol solution (pH 7.0) containing 0.052% (w/v) methyl p-hydroxybenzoate, 0.028% (w/v) propyl p-hydroxybenzoate, 0.1% (w/v) polyvinyl pyrrolidone (COLIDONE (registered trademark) 30, available from BASF Aktiengesellschaft) and 0.01% (w/v) EDTA.2Na, there was added an equal volume of the CB emulsion according to the formulation 100 whose pH was adjusted to 7.0 followed by sufficient mixing. The mixture was then filtered through a membrane having a pore size of 0.8 .mu.m to thus prepare a CB emulsion containing the foregoing additives. The resulting emulsion was filled in an eye drop bottle, then thermally sterilized according to the fractional sterilization method to thus give an eye drop of the present invention.

Detailed Description Text (130):
To a 2% aqueous glycerol solution (pH 8.0) containing 0.052% (w/v) methyl p-hydroxybenzoate, 0.028% (w/v) propyl p-hydroxybenzoate, 0.1% (w/v) polyvinyl alcohol (degree of polymerization 2000, available from Wako Pure Chemical Co., Ltd.), 0.1% (w/v) histidine and 0.04% (w/v) sodium citrate, there was added an equal volume of the CP emulsion according to the formulation 222 followed by sufficient mixing. After adjusting the pH of this mixture to 8.0 with NaOH, it was filtered through a membrane having a pore size of 0.8 .mu.m to thus prepare a CP

emulsion containing the foregoing additives. The resulting emulsion was filled in an eye drop bottle, then thermally sterilized according to the fractional sterilization method to thus give an eye drop of the present invention. Moreover, the resulting eye drop of the present invention and Ageless (registered trademark) Z (available from Mitsubishi Gas Chemical Co., Inc.) were packaged together in a laminate bag of a polyethylene film and an aluminum foil according to the pillow-packaging technique.

Detailed Description Text (132):
To a 2% aqueous glycerol solution (pH 7.0) containing 0.052% (w/v) methyl p-hydroxybenzoate, 0.028% (w/v) propyl p-hydroxybenzoate, 0.1% (w/v) polyvinyl pyrrolidone (COLIDONE (registered trademark) 30, available from BASF Aktiengesellschaft) and 0.01% (w/v) EDTA.2Na, there was added an equal volume of the CP emulsion according to the formulation 222 whose pH was adjusted to 7.0 followed by sufficient mixing of the resulting mixture. The mixture was then filtered through a membrane having a pore size of 0.8 .mu.m to thus prepare a CP emulsion containing the foregoing additives. The resulting emulsion was filled in an eye drop bottle, then thermally sterilized according to the fractional sterilization method to thus give an eye drop of the present invention.

Detailed Description Text (145):
(Preparation of Sample) There was prepared a CB emulsion containing 0.04% (w/v) CB, 0.4% (w/v) phospholipid [EPC:PYL=7:3 (weight ratio)], 20% (w/v) liquid paraffin and 2% (w/v) glycerol by the same method disclosed in Example 9. To the resulting emulsion, there was added an equal volume of a 2% aqueous glycerol solution (pH 7.0) containing 0.052% (w/v) methyl p-hydroxybenzoate, 0.028% (w/v) propyl p-hydroxybenzoate and 0.01% (w/v) EDTA.2Na followed by sufficient mixing thereof. After adjusting the pH of the mixture to 7.0 with NaOH, the solution was filtered through a membrane having a pore size of 0.8 .mu.m and then filled in an eye drop bottle. Thereafter it was thermally sterilized by the fractional sterilization technique to thus give a CB emulsion eye drop according to the present invention.

Detailed Description Paragraph Table (8):
TABLE 7 Phospholipid Liquid Paraffin CB Concn. Formulation % (w/v) % (w/v) % (w/v)
99 0.30 24.0 0.01 100 0.20 9.00 0.02 101 0.40 18.00 0.02 102 0.90 25.00 0.03 103 Suspension 0.1 Dissolved CB Concn. (.mu.g/ml) Dilution Factor Formulation 21 41 101
99 0.41 0.35 0.30 100 1.08 0.87 0.68 101 0.61 0.46 0.32 102 0.33 0.22 0.12 103 0.24 0.17 0.09
Dissolution Test: The CD emulsion was diluted from 21 to 101 times with PBS. Phospholipid: EPC:PYL = 7:3 (weight ratio) Suspension: CLOBURATE (registered trademark) (CBsuspended eye drop, 0.1% (w/v) CB, available from Cusi (UK) Ltd.)

Detailed Description Paragraph Table (9):
TABLE 8 Phospho- Liquid CB Dissolved lipid Paraffin Concn. CB Concn. Formulation % (w/v) % (w/v) % (w/v) (.mu.g/ml)
104 0.008 0.36 0.0008 0.10 105 0.012 0.54 0.0012 0.17 106 0.025 1.13 0.0025 0.15 107 0.05 2.25 0.005 0.30 108 0.06 2.70 0.006 0.56 109 0.10 4.50 0.01 0.68 100 0.20 9.00 0.02 0.87 110 0.50 22.50 0.05 0.98 111 0.40 4.00 0.02 0.35 112 1.00 10.00 0.05 0.36 113 1.60 16.00 0.08 0.25 114 2.00 20.00 0.1 0.21 115 0.60 6.00 0.02 0.27 116 1.50 15.00 0.05 0.28 117 3.00 30.00 0.1 0.23 103 Suspension 0.1 0.17 Dissolution Test: The CB emulsion was diluted 41 times with PBS. Phospholipid: EPC:PYL = 7:3 (weight ratio) Suspension: CLOBURATE (registered trademark) (CBsuspended eye drop, 0.1% (w/v) CB, available from Cusi (UK) Ltd.)

Detailed Description Paragraph Table (21):
TABLE 18 Phospho- Liquid CB Dissolved lipid

Paraffin Concn. CB Concn. Eye Drop %(w/v) %(w/v) %(w/v) (.mu.g/ml)
CB Emulsion 0.2 10 0.02 0.67 Eye Drop Suspension having -- -- 0.1 0.17 Formulation 103 (CLOBURATE)
Dissolution Test: The CP emulsion was diluted 41 times with PBS. Phospholipid: EPC:PYL = 7:3 (weight ratio) Additives Included in the CB Emulsion Eye Drop: methyl p-hydroxybenzoate 0.026% (w/v) propyl p-hydroxybenzoate 0.014% (w/v) disodium ethylenediaminetetraacetate 0.005% (w/v) glycerol 2% (w/v) Time Elapsed after Dropping in the Eyes(min) Eye Drop 5 30 120
CB Concn. in Conjunctiva: .mu.g/g (S.D.) CB Emulsion 0.98(.+-.0.14)** 0.20(.+-.0.08)* 0.00 Eye Drop Suspension having 0.10(.+-.0.07) 0.07(.+-.0.06) 0.12(.+-.0.11) Formulation 103 (CLOBURATE)
CB Concn. in Cornea: .mu.g/g (S.D.) CB Emulsion 1.43(.+-.0.21)** 0.71(.+-.0.19)** 0.14(.+-.0.03) Eye Drop Suspension having 0.09(.+-.0.03) 0.07(.+-.0.02) 0.07(.+-.0.03) Formulation 103 (CLOBURATE)
CB Concn. in Aqueous Humor: ng/ml (S.D.) CB Emulsion 0.00 4.57(.+-.1.78)** 4.60(.+-.1.19) Eye Drop Suspension having 0.00 0.38 (.+-.0.75) 1.17(.+-.1.13) Formulation 103 (CLOBURATE)

Current US Original Classification (1):
424/422

Current US Cross Reference Classification (1):
424/427

Current US Cross Reference Classification (2):
424/428

CLAIMS:

1. An O/W emulsion composition for eye drops, consist essentially of a drug selected from the group consisting of fluorometholone, clobetasone butyrate and clobetasol propionate; a phospholipid; liquid paraffin; and water.

Previous Doc Next Doc Go to Doc#

L19: Entry 74 of 82 File: USPT May 5, 1998

DOCUMENT-IDENTIFIER: US 5747061 A
TITLE: Suspension of loteprednol etabonate for ear, eye, or nose treatment

Brief Summary Text (4):
Numerous drugs are prepared in the form of suspensions for ophthalmic, oral, otic, nasal respiratory is topical, and parenteral applications. Formulation of pharmaceutical dosages of water-insoluble drugs as suspensions is frequently hampered by the subsequent formation of cakes resulting from aggregation of the suspended material. Polymeric compounds (e.g. polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), dextran) are commonly used to stabilize such suspensions. An alternative approach to the preparation of such drugs is to enhance the solubility of the drugs within the formulation by vehicles including emulsions, liposomes, and cyclodextrins. However, certain drugs, in their therapeutic concentrations, are not sufficiently stabilized or solubilized by these methods for the above-mentioned applications.

Brief Summary Text (9):
Therapeutic suspensions of corticosteroids typically employ polymeric compounds such as polyvinyl pyrrolidone ("PVP") and polyvinyl alcohol ("PVA") as suspending agents in concentrations ranging from 0.1 to 10% (U.S. Pat. No. 2,861,920). Combinations of polymeric compounds such as PVP, PVA, sodium carboxymethylcellulose ("CMC"), and dextran, with surface-active agents such as Polysorbate 80, Polysorbate 20, and tyloxapol also have been used to stabilize corticosteroid suspensions intended for ophthalmic, nasal, and otic uses.

Detailed Description Text (29):
The soft steroid loteprednol etabonate was formulated as an aqueous ophthalmic suspension containing polyvinyl pyrrolidone (0.6%), glycerine (2.4%), tyloxapol (0.3%), edetate disodium (0.01%) and benzalkonium chloride (0.01%). Loteprednol etabonate (0.5%) was incorporated into this vehicle for use in clinical studies. During these studies, the formulation was evaluated on a total of 446 patients, 220 of which had giant papillary conjunctivitis ("GPC"), 145 of which had seasonal allergic conjunctivitis ("SAC") and 81 had acute anterior uveitis.

Current US Original Classification (1):
424/427

Current US Cross Reference Classification (1):
424/434

Current US Cross Reference Classification (2):
424/437

CLAIMS:

5. The composition of claim 2 wherein said nonionic polymer is a water soluble polymer selected from the group consisting of polyvinylpyrrolidone, polyvinyl alcohol, dextran and cyclodextrin.

22. The composition of claim 1 wherein said nonionic polymer is a water soluble

polymer selected from the group consisting of polyvinylpyrrolidone, polyvinyl alcohol, dextran and cyclodextrin.

Previous Doc Next Doc Go to Doc#

L19: Entry 75 of 82 File: USPT Dec 2, 1997

DOCUMENT-IDENTIFIER: US 5693337 A
TITLE: Stable lipid emulsion

Abstract Text (1):
A lipid emulsion which comprises (A) an oil component, (B) an emulsifying agent containing yolk lecithin and/or soybean lecithin, and (C) water, wherein the lipid emulsion further comprises citric acid or a pharmaceutically acceptable salt thereof and at least one member selected from the group consisting of methionine, phenylalanine, serine, histidine and pharmaceutically acceptable salts thereof, provided that it does not simultaneously contain methionine and phenylalanine. The addition of citric acid and histidine, methionine, phenylalanine and/or serine to a lipid emulsion containing natural lecithin as an emulsifying agent permits the prevention of change of color and formation of oil drops associated with the conventional natural lecithin-containing lipid emulsion due to the synergistic effect of the foregoing additives. The drug-containing lipid emulsion is also excellent in storage stability and thus the foregoing lipid emulsion can be applied to drugs such as injections, eye drops, nasal drops, lotions or liniments, inhalants and drugs for oral administration or cosmetics such as humectants.

Brief Summary Text (83):
When the lipid emulsion of the present invention is processed into preparations such as those discussed above, it is possible to add, to the preparations, isotonic agents such as saccharides or glycerin; pH-adjusting agents; antiseptic agents such as methyl p-hydroxybenzoate and propyl p-hydroxybenzoate; thickening agents such as methyl cellulose, polyvinyl pyrrolidone or sodium polyacrylate; and/or stabilizers such as albumin, dextran, polyethylene glycol or gelatin, in such an amount that the intended effect of the present invention is not impaired.

Current US Original Classification (1):
424/450

L19: Entry 77 of 82 File: USPT Jul 30, 1996

DOCUMENT-IDENTIFIER: US 5540930 A
** See image for Certificate of Correction **
TITLE: Suspension of loteprednol etabonate for ear, eye, or nose treatment

Brief Summary Text (4):
Numerous drugs are prepared in the form of suspensions for ophthalmic, oral, otic, nasal respiratory topical, and parenteral applications. Formulation of pharmaceutical dosages of water-insoluble drugs as suspensions is frequently hampered by the subsequent formation of cakes resulting from aggregation of the suspended material. Polymeric compounds (e.g. polyvinyl pyrrolidone, polyvinyl alcohol, dextran) are commonly used to stabilize such suspensions. An alternative approach to the preparation of such drugs is to enhance the solubility of the drugs within the formulation by vehicles including emulsions, liposomes, and cyclodextrins. However, certain drugs, in their therapeutic concentrations, are not sufficiently stabilized or solubilized by these methods for the above-mentioned applications.

Brief Summary Text (9):
Therapeutic suspensions of corticosteroids typically employ polymeric compounds such as polyvinyl pyrrolidone ("PVP") and polyvinyl alcohol ("PVA") as suspending agents in concentrations ranging from 0.1 to 10% (U.S. Pat. No. 2,861,920). Combinations of polymeric compounds such as PVP, PVA, sodium carboxymethylcellulose ("CMC"), and dextran, with surface-active agents such as Polysorbate 80, Polysorbate 20, and tyloxapol also have been used to stabilize corticosteroid suspensions intended for ophthalmic, nasal, and otic uses.

Current US Original Classification (1):
424/427

Current US Cross Reference Classification (1):
424/434

Current US Cross Reference Classification (2):
424/437

CLAIMS:

8. The composition of claim 1 wherein said nonionic polymer is selected from the group consisting of polyvinylpyrrolidone, polyvinyl alcohol, or dextran and is present in an amount of about 0.2 to 2% by weight and wherein the nonionic surfactant is present in an amount of about 0.05 to 1% by weight.

17. The composition of claim 13 wherein the nonionic polymer is polyvinyl pyrrolidone and is present in an amount of about 0.4 to 1% by weight, the nonionic tonicity agent is mannitol or a diol and is present in an amount of about 2 to 2.8% by weight, and the nonionic surface active agent is tyloxapol and is present in an amount of about 0.1 to 0.6% by weight.

L19: Entry 79 of 82 File: USPT Jun 13, 1989

DOCUMENT-IDENTIFIER: US 4839175 A
** See image for Certificate of Correction **
TITLE: Liposomes with enhanced retention on mucosal tissue

Abstract Text (1):
A liposome composition designed for enhanced binding to mucosal tissue, The liposomes contain about 10-40 mole percent of an amine-derivatized lipid component in which a charged amine group is spaced from a lipid polar head region by a carbon-containing spacer arm at least 3 atoms in length. The liposomes preferably have a close packed lipid structure produced by inclusion of between 20-50 mole percent of cholesterol or an amine-derivatized cholesterol, and/or phospholipids with predominantly saturated acyl chain moieties. For ophthalmic use, the liposomes may be suspended in an aqueous medium containing a high-viscosity polymer, to enhance further the retention of liposomes on a corneal surface.

Brief Summary Text (40):
Still another object of the invention is to provide an improved liposome composition for the treatment of dry eye.

Brief Summary Text (51):
The liposome composition may further be formulated for increase retention near the tissue site (as well as increased retention to the mucosal tissue). For ophthalmic uses, the formulation may include increase-viscosity polymers. For uses in body cavities, the liposome may be formulated for delayed release in suppositories or slow-release polymer matrices. Aerosolized liposomes for nasal and oral drug deliverly, and cream or foam formulations for topical application are also disclosed.

Brief Summary Text (53):
In still another aspect, the invention includes a method of treating dry-eye, by applying to the ocular surface, a preferably optically clear suspension of positively charged liposomes of the type described above. The suspension may contain increased-viscosity polymers for greater liposome retention at the ocular site. The liposomal lipids contribute to the lubricating properties of the dry-eye composition.

Detailed Description Text (40):
Still anothe consideration in the choice of the lipid components is extent of lipid oxidative/peroxidative damage which can be tolerated. It is known, and experiments conducted in support of the invention have confirmed, that both unsaturated phopholipids and cholesterol are susceptible to lipid oxidative damage, particularly where the lipids are stored over an extended period at above refrigeration temperatures. The problem of lipid oxidation damage would therefore be quite sever for a lipsome product, such as an ophthalmic eye-drop composition, which is normally sold and stored at room temperature. Reduced oxidation can be achieved by using predominantly saturated lipid components, such as saturated phospholipids and diglycerides and cholestane sterols.

Detailed Description Text (48):
Either the REV or MLV preparations can be further treated to produce a suspension

of smaller, relatively homogenous-size liposomes, in the 0.1-1.0 micron size range. Advantages of smaller, more homogeneous-size liposomes are: (1) more uniform drug release properties, (2) higher density of liposome packing allowed at a mucosal tissue surface, and (3) greater optical clarity in ophthalmic applications. One effective sizing method involves extruding an aqueous suspension of the liposomes through a polycarbonate membrane having a selected uniform pore size, typically 0.2, 0.4, 0.6, 0.8 or 1 microns (reference 3e. The pore size of the membrane corresponds roughly to the largest sizes of liposomes produced by extrusion through that membrane, particularly where the preparation is extruded two or more times through the same membrane. A more recent method involves extrusion through an asymmetric ceramic filter. The method is detailed in co-owned U.S. patent application for Lipsome Extrusion Method, Ser. No. 829,710, filed Feb. 13, 1986 and now U.S. Pat. No. 797,285.

Detailed Description Text (49):
Alternatively, the REV and MLV preparations can be treated to produce small unilamellar vesicles which are characterized by sizes in the 0.04-0.08 micron range. Because of the small particle sizes, SUV suspensions can be optically quite clear, and thus advantageous for ophthalmic applications. Another advantage of SUVs, as suggested above, is the greater packing density of liposomes on a mucosal surface which can be achieved with smaller liposome particles. This feature is valuable, for example, in one of the novel uses of the invention, where the liposomes are used as an ocular lubricant in the treatment of dry eye.

Detailed Description Text (58):
The aqueous liposome suspensions prepared as above are suited to ophthalmic uses in which the liposomes are applied in droplet form to the eye. For ophthalmic use, the liposomes are preferably sized, relatively small REVs or MLVs, or SUVs, typically at lipid concentrations of between about 5 and 50 .mu.mole lipid/ml.

Detailed Description Text (59):
As indicated above, the retention of liposomes on mucosal tissue can be enhanced by including in the suspension, high molecular weight polymers which act to increase suspension viscosity. Typical polymers for use in ophthalmic formulations are methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and polyvinylalcohol. The effect of these polymers on ocular retention wsa examined in the studies reported in Example XI. In a first study, SUVs prepared with either 20 mole lysinyl PE or lysine lysinyl PE were formulated in a dilute suspension of buffer alone or buffer containing 0.8% hydroxyethylcellulose and 0.2% polyvinylalcohol, and ocular retention over a 1 hour period was measured. As may be seen, addition of polymers (solid symbols) significantly increased the level of liposome retention after 1 hour in both lysinyl PE SUvs (circles) and in lysine lysinyl PE SUVs (triangles).

Detailed Description Text (63):
The liposomes suspensions are also useful in ophthalmics for treating dry eye. This condition, which is characterized by poor moisture retention on the eye, has a number of distincy eitologies, including poor water-secretion by the lacrimal gland (Sjogren), poor mucin secretion by goblet cells (Lemp), vitamin A deficiency (Lawrence), and alteration of film-forming lipids as a result of chronic blepharitis. These are primarily long-chain alcohols and acids and cholesterol esters, which are required for forming a stable preocular tear film (Anderson).

Detailed Description Text (64):
Conventional dry eye formulations are polymer solutions which provide, when applied to drop form, a film of moisture which has increased retention on the eye by virtue of the solution viscosity. The liposome formulation of the present invention provides three important advantages over these earlier formulations. First, the liposomes in the suspension are retained on the eye in appreciable quantity for several hours, in contrast to viscous solutions which are largely cleared after 1

hour. Second, the surface-bound liposomes provide a matrix for holding encapsulated and bound aqueous fluid. Third, the liposomes themselves can be formulated to supply necessary lipids needed for film formation. Long-chain alcohols and fatty acids, and cholesterol esters which make up the films are all compatible with stable vesicular structures. Further, experiments conducted in support of the present invention indicated that the aqueous ocular environment contains phospholipases capable of deacylating phospholipids to yield long-chain fatty acids.

Detailed Description Text (65):
Several considerations are important in formulating a liposomal suspension for dry eye treatment. One preferred lipid composition contains lipid components designed to contribute to film forming on the eye surface. For example, the phospholipid components can be selected to yield optimal long chain fatty acids after hydrolysis. Small amounts of long chain alcohols after hydrolysis. Small amounts of long chain alcohols and fatty acids can also be included without destabilizing the liposomes appreciably.

Detailed Description Text (68):
Still another consideration is achieving good optical clarity in a liposome/polymer suspensions. In addition to liposome size, which is discussed above, the liposomes and polymers must be stable in terms of aggregate effects, such that if aggregation occurs, the liposome/polymer complexes can be easily dispersed by shaking. For both of the hydroxyethylcellulose/polyvinylalcohol, and NEO-TEARS.TM. polymers used in formulating ophthalmic liposomes, good optical clarity after two months storage at room temperature, and clouding which was observed could be cleared by moderate shaking.

Detailed Description Text (82):
In another therapeutic use, the enhanced-retention liposomes provide several advantages over polymer solutions for treating dry eye.

Detailed Description Text (181):
In vivo ocular retention studies were performed in rabbit eyes using a scintillation probe technique. In each experiment, 10 .mu.l of liposomes containing about 100 nmole lipids and 10.sup.5 cpm of .sup.125 I-labeled PE were applied to the rabbit eye. Retention was assessed with the gamma probe positioned over the eye. A constant distance between the probe and the eye of 2 cm was insured by fitting the probe into a plexiglas sleeve-holder. A 1/8 inch thick lead partition placed against the lacrimal-nasal region of the rabbit effectively blocked radioactive material which drained into the nasolacrimal region. Retention time was monitored over a period of 1 hour unless specified otherwise. From the chart recordings, peak height readings were obtained. Total radioactivity of each reading was calculated from a standard curve by in vitro measurements of standard dilutions of the radioactive liposomes. Percent retention was calculated based on counts per minute (CPM) of the original 10 .mu.l sample.

Detailed Description Text (184):
In a second study, the effect on ocular retention of increasing amounts of lysinyl-lysinyl PE in SUVs was investigated. The four SUV preparation studies contained 40 mole percent cholesteryl, 10, 20, or 30 mole percent lysinyl-lysinyl PE, and remainder amounts of egg PC. A control, containing cholesterol and egg PE in a 40:60 mole ratio, was the same as above. The study was performed as above, by applying 100 .mu.l of liposomes (about 100 nmoles) to the rabbit eye, and measuring the remaining counts with a gamma counter at five-minute intervals after administration. The results are shown in FIG. 2, where the control is indicated by solid squares, and SUVs with 10, 20, and 30 mole percent lysinyl-lysinyl PE, by open circles, closed triangle, and open squares, respectively. Consistent with the above results, increasing amounts of the doubly charged PE gave increasing retention. In general, and particularly for the 20 mole percent doubly-charged

liposomes, the retention times are significantly higher than for the corresponding concentrations of singly charged PE SUVs.

Current US Original Classification (1):
424/450

Current US Cross Reference Classification (2):
424/1.21

Current US Cross Reference Classification (3):
424/427

Current US Cross Reference Classification (4):
424/428

Other Reference Publication (5):
H. E. Schaeffer and D. L. Krohn. Titled: Liposomes in Topical Drug Delivery, pp. 220-227, Invest. Ophthalmol. Vis. Sci., Feb. 1982, 0146-0404/82/020220.

CLAIMS:

8. The method of claim 1, for use in treating dry eye, wherein the phospholipid components in the liposomes are predominantly saturated in acyl chain moities, and which further includes applying the liposomes to the corneal surface of the eye.

10. The method of claim 8, wherein the liposomes are contained in a suspension medium containing polymers selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, polyvinyl pyrrolidone, and polyvinylalcohol.

Previous Doc Next Doc Go to Doc#

L19: Entry 82 of 82 File: USOC Jul 28, 1959

DOCUMENT-IDENTIFIER: US 2897120 A
TITLE: Low viscosity cmc pharmaceutical vehicle

OCR Scanned Text (2):
of the two or like hydrophiiic poiyvinyi co ounds, wiih MP a low viscosity alkaline salt of carboxymethylcellulose would give markedly superior suspensions. The superior suspending propertie's of such combinations o,f hydrophilic polyviiiyl. compounds and a low viscosity alkaline salt of . carb6xyiiiieihylcellulose coupled with WLher factors which complement or enhance the siispending action of the combination, such as the particle sL7e of the insoluble materials u,iiized, the pH of &.e vehicle, the viscosity of the vehicle, the coatings on the insoluble medicinal a,@ents involved, the amotint of insoluble medicinal a.-ent utiliz-.d, the coating on Lie bottles or containers from which the suspension is to be dispensed, and the preservative used where the s,.lspe@isioTi mlist be sterile for parenteral adrninistratio@-i, prol@ide suspensions suitable for fberapeutic use which avoid difficulties heretofore encountered in the prior art. The oresent invention, therefore, is directed broadly to the use of a combination of a hydrophilic polyvinyl compouiid, such as polyvinyl pyr.-olidone, polyvinyl alcohol, and mixttires thereof, and a low viscosity alkaline salt of- carbo-,I,.-nethylcellulose, such as the low viscosity sodi-Lim and ot Tier alkali metal salts of carbo-,ymethylcelItilose, as a suspending agent for an insoltible medicinal agent in an aqueous velicle and more particularly to combinations embodying various of the other factors noted above as will be more particularly set fo-rth hereiiiafter. One of the more important factors wliich may be used to- comnlement or enliance the combination suspending agent of the invention is t'tie viscosity of the suspension. Thus it has been found advantageous in preparing suspensions according to the itivention to maintain a viscosity of about fifteen to about ei,-hty centipoises at room temperatlire and that opti-tnum results are obtained ordinaffly with a viscosity belween abo-Lit twenty and forty centipe-ises at roor@i tpmperature. While several factors affect the viscosity of the suspensions, the amotint of the hydrophilic polyvinyl compound, the amount of the low viscosity alkaline salt of carbox ymethylcellulose, and the amount and character of the active material, that is, the insoluble medicinal a.-ent wbich is to be suspended, and while the viscosity can sometimes be affected by the addition of sutface-active agents and deflocciilating agents, suitable viscosities are ordinarily obtained by the use of from aboiit 0.1 to about three percent of polyvinyl pyrrolidone (percentages here weight by volume unless otherv,iise specified), and about 0.1 to about one percent of a low viscosity alkali salt of carboxymethyleellulose. The term "low voscosity alkaline salt of carboxYmethYlcellulose" is iised herein to designate those alkali carboxymetllylcelluloses, siieh as sod;um carbo-,-,ymethylcellulose, which have a viscosity in two pcrcent aqueous solution of less t@ian abotit 100 centipoises and advantageously between about 25 ar@d fifty ce-@itipoises at 25 degrees centi,-rade usin.- a Brookfield Viscometer Model LVF. T-hiis by combi-12ing betiveen aboi-it 300,000 and about 600,000 units of procaine penicillin per milliliter of suspension, advanta,-,t-,otisly about 500,000 iipits per ntilliliter, vitli about 0.5 -ocrcent polyvinyl pyrrolidone and abolit 0.5 percent of I-ow viscosity sodium carboxymethylcellulo:-,e, there are obtained suspensions which Nvhen pret)ared asertically are particiilarly wel' . suited for

J)arenteral -u.-se a@-id which can be injected through a 'iypodermic needle wthoit tic disadvantages heretofore et,cotintered in this art. is to -Lise fifty peycejit of microTt is rr@ost advapta?,eol nized nr(-.caine penicillin having a partir-le size ranging from t'.vo to tei, microns together witli fifty perr-ent milled procaine pericillin with a particle size ranginl@ from forty to sixty microns. The exact reason for the improved suspensions obtained by using particles of varying sizes is not known, but some- obser,,ations re-arding the pro- @verties of such suspensions hw;e been made. For example, it has been obser@,!@d t]@at small particles apparently in- 2i897,120 crease ihe v@ cosiiy oi ihe vehicle andtend to form agis gregates or globules of the active ingredient. When all par-ticles are of the same size, they seem to have a greater _ tendency tp pack. Whe,n thd suspension is prepared fof injectign through d syririg6, ihe use of particies of thd same size tends io 6iehte a soft o@ log jam when passing through the needle. Ther6 seems io be a lesser tendency to block a needle when the particles are of varying sizes. It has been observed that eighteen to 26 gauge needles lo can be used when the paxticles are of the varying sizes indicated. Of course, it is not absolutely essential to the present invention to have varying particle sizes of between about two to sixty microns of the active medicinal agent to be suspended, 'but more consistent restilts I r) will be obtained if varying particle sizes are used. Further improvement is obtained by coating the insoluble material to be suspended with a phospholipid, such as lecithin, cephalin and the like. This is the subject matter of copending application Serial Number 108,419, 20 filed ALigust 3, 1949, now Patent Number 2,694,665, issued November 16, 1954. Thus lecithin coating has been successfully utilized on procaine penicillin. Although the role of the phospholipid as a coatin.- for the insoluble medicinal agent in the compositions of the present in- 25 vention is more fully explained in the copending application indicated, it should be noted that such coated materials contribute rnuch to the success of suspensions st,.ch as dealt with in the present invention. Besides-contributing to the overall qualities of the susperi-sion, a phos- 30 pholipid coating seems to act as a sort of dispersing a,-erit forthe insoluble medicinal agent. Without such a coating procaine penicillin particles, for example, do not wet properly. However, any such observation as to the contribution of lecithin to the preparation of a successful 35 suspension will not withstand critical scrlitiny. It is only important to note that lecithin does contribute to the overall success of the suspension, both as an individual ingredient and in cow-bination with the other materials indicated. 40 Depending upon the natiire of the insoluble medicinal agent to be suspended, it may prove desirable to util;ze a buffer to control the pH of the suspension within a desired range. For example, it is desirable to tise sodium citrate where procaine penicillin, cortisone acetate, hydro- 45 cortisone, hydrocortisone acetate and similar materials are to be suspended. For procaine penicillin it is desirable to use sufficient buffer to kee@i) the supension close to but beloiv a pH of about 7, that is between about 5 and about 7. It should also be noted that the pH may chan,@e upon storage depending uinon the temperalure. For example, if the pH starts out at about 6.3 to 6.5, it will probably go down to about 5.5 to 5.8 tipon storage at room temperature for ony considerable length of time. Further improvement for the suspensions of ti@e p@-es-55 c-@it inve-@ition can be obtained by the use of silicone coated bottles as containers tberefor. These tend to impart proper wetting characteristics to the surface of glass fron which such suspensions are dispensed. From this stand-ooint it should be noted that the vehicle of the present in- (,,O 'vention works in a very satisfactory maniier, in sflicone coated bottles, while vebieles containirig such surface ap-tive materials as Tween 80 (a polyoxyetbylone etl,.er of a partial higher fatty acid ester of sorbitan) so affect the silicone coating as to give undesirable results. For ex- C) 5 ample, a silicone coated bottle containing such a slrf ace active agent causes a haze in the bottle and clouds it in such a way as to cbscure its contents, tends to indicate poor drainage, or give the impression of a contaminated 70 product. When the suspensions of the present invent;oi are titilized for sterile purposes, such as for parenteral injection, it is desirable to -L7tilize a preser-vative such as metbyl, propyl, or butyl parabens. AlthoLgh sucii preservatives 7 c-) do not contriblte anytling to the susper@sion of

insollble

OCR Scanned Text (3):
2,897,120 5 niedicinal agents, they are @l@o not adversely affected by the vehicle utilized in the present invention. The phrase "procaine penicifl&'.is used. in the present- specific.qtion in a generic sense@ and is intended to include the various forms of penicillin, such as G, 0, K and the like, as well,as other deriVativVes,of procaine, such as- 2chloroprocaine, wliieh are capable of forniing insoluble salts with pelnici.Ilin. Likewise other insoluble penicillin salts such as N,N-dibenzylethylenediamine. veniciwn. are successfully suspended by ihe'v'ehi@le,@of the piesent in- io vention. It will be appa'rent ff6ni tbe@ ididgciing 'that a considerable number of variables can and are @involved @in preparing successful suspensions such as contemblated by the present invention. Numerous eiperimeiits have @15 been conducted in an'attem@t io,@djust'the'-@ariabl@s to prepa,re the most successful product. Waffe there is little doubt that the basic combination of a hydrophilic poly,vinyl compound,and a low viscosity alkaline salt of carboxymethylc6llul6se is ihe ifto@t import@iit:;or fiinda'meii- @o tal factor in the present invention, the -other f@ctors indicated are defl-,mte improvements thereof. Among the numerous experimeiits conducted with the vehicle of the present invention are the following, pre- sented in summarized form: 25 I Results obtai@ed Materials iised Comparison of sodium c I grboxy@ Vehicles of vailous @coiie I entratiohs methyleelltilose (OMC) of dif- plus procaine penicillin G wore 30 ferent viscosities, high, medi- evaluated on the basis of suspend- um, lo,,v, with the - addition of Ing quality and d ina?e in sili6one polyvihyl pyrr6lidone (PVP) treated bottles, Td 3 results in- at one percent concentration. dicated that s@spensions with. so- dium carboxymethyl6e]li@ldse @lone did not drain as ivell as'susp6mi6ns with sodium caibox@meth@,leell@i- lose (CMC) and polyviiayl pyrroli- 35 done '(PVP) oiily low @@isco@ity, CM C was suitable Comparison of vario,,is combina- Resuspending qualities of suspen- tions of procaine penicillin G sions made with vehiole contatuing 300,000 anits/ec. and PVP ve- PVP without CM O wero generally bieles (1%). pogrer (packing, settling, and re-, suspendabiuty) than those suspen- 40 sions made with OMC and PVP. Aqueous suspension of 2-chloro- Resultant susperision would not procaine penicillin 0 300,000 1 readily resuspend. units/cc. aiad PVP vehicl6 (1%). Aqueous susl3@it@ion of @r66aine This'su's'pension'would iiot re@dily penicillin G 300,000 units/cc. in resuspend after three weeks storage 6 boxymethylcellulose. SimilAr results are obta@med by us@@ mg polyvinyl alcohol and other alkaline salts of carboxymethyl@ellulose. The polyvi ' nyl hydrophihe-compounds-of the inven. tion, @are'-of 'pb- 'arin'aceutical -gi@de, 'n'6ii-;Ioxic, inert and capitble of being st6ri@Iiied wit]Yout change in composition. @ bn'the @i'dditioii,6f *dt6r' tb a dry @dh*i-)iitibn containing a st6roid and- ihe @select6d hydrophilic polyvinyl compound, followed by m'ixing, a stable steroid suspension is readily obtained. The polyvinyl pyifblidone used in the coxilp6sitions described herein is sold @by'-the - General Anilme -aiid Fihn Company under the trademark "Plasdone' and is characterized by a viscosity coefficient, i.e., K value, of 26 to 36 6iid a moierular- w6i@ht 'Of'.itb6iit 40@000. However, it 'is to b6 understo6d'Ithat the-iiiveiition@-is ;iiot to be liniited to the use @of@ this s@edific polyvinyl pyrrolidone since other equivgent p6lyvinyl @yii76Jiddji&s 6f pharmaceutical grade. are likev@ise suit@ble, While ,a polyvinyl -pyrrolidcine of pharmaceutical grade -poss6ssing a molecular weight between, twenty and ei I ghty thousand is preferred, sdtisfactory results are also - obtained- by the use of a polyvinyt pyrr6lidone oiltside of thig molecular - weight range. The pol@@fiyl -,alcohol utilized in the compositions des ed h6iein is sold by the Du Pont Company'under the trademark "Elvanol" 51-05 and is characterized 'by- a viscosity of fodr to six ctnti@oises (four porpent. aqupous solution at twenty degrees centigrade), a pH of six to eight ajid a 86 t6 89 percent hydtbrysis from poly@,inyl acetate. It is to- be uiiderstooa, ho-wever, that the -invention is not Iiii6ited tb the'use of this specific' p613@Vbiyl alcohol @ince any oth&r ' equiv@lent polyvinyl. alcohol of pharmaceutical grade-can, Ekemiise be used to achieve siniilar results. Sirilil@,r 6@.periments ahd' siiiiilar k@stift@@-have- b&en obtained--with the basic c6nibin@ation-of- a

hydrophilic-@olyvinyl cbnip6und witli e@ 16w Vi@c6 ity dlkiiriiie dlt'6f carboxymethyleellulose in an aqueous vehicle - -for bther in@oluble; medicin I al e e owing , a@&iits. Por 6i;i*1 , ih - -foll- - tables - demonstrate the use of the aforesaid veP@icle@'for various st6ioids sudh' as cottis6n6 a-ce-t-ate,-- hydrocortisone, and hydroc6rtisone acetate, The Vehiel6@ are rated in @the ta@bles :by an arbitrairy scale rangini from "'O" to @'4-@ penicilliii G 500,000 units/cc. in sically at room t6mperature for five PVP vehicle (1%). months, At five and - one-balf montbs it bad settled enough to give poor syriiig6gbility i6gults. Aqueous suspension of procaine This suspension remained stable at penicillin G 500,000 units/cc. in room temperature foi, eight moiiths PVP (1%)-LV'CMC (0;2%) and is easily b'ected. Th:e samples 50 vebicle. of this sil@p'elision gtored 'iia the, ie- frigerator for eight months are easily@s"ged and have not pack- ed or hettled out. 1,000,000, unit vial of procaine The powder, When constituted, gives penicillin G (800,000 units) and a'suspeiision of excellent drainage, sodium penicillin G (200;000 gdod . resuspendability and good 55 units) witb 0.5% LV OMO and sytlngeability. 0.6% PVP. Aqueous suspension of procaine Visebsity of this suspension was low penicillin G 300,000 uixits/ce. and the inaterial settled out and in 1% PVP vehicle. packed. Aqueous snspension of procaine T,his suspension had a low. viscosity penicillin G 300,000 units/ec'lin aud good drainage and resuspend- 60 PVP (1%) and LV Omo abuity. (0.5,@,). Aqueous suspei2sion of procaine Visdosit@ of this - suspension was high ppi2icillin G 300,000 units/cc. in (128'cps.) and gave poor'drainage. LV OMO (0.5%) vehicle. - Various suspemsioias ilsing PVP VarioUs suspeiasions in vialg. have -'K alone, LV CMC alone, and b@@n shipped from alainazocl. PVP + LV CMC . Alichigan to Los-Angeles Min@ 65 neapolis and Atlaiita by! train, plane, and track. - Evaluotion of samples on return sbows that the PVP-LV OMO vebicle gives a i@roduct with good drainage, good resii pendability,-snd good syrin@efibflity while neither PVP alone 70- nor CMC alone does. *Loiv viscosity material which at 2%. concentration in aqueous solution has a viscosity of 25 to 50 centipoises at 251 C. PVP vehicle (10/,). at room temperature (251 C.). @ - 45 -The preparations were graded for such chararteristics Aqueous suspension of procaine This suspension remained stable phy- as appeara nce, -resuspendability, syringeability, drainage and changes in particle size. A pr- eparation with-an @'O" rating is entirely unacceptable and indicates physical in- stability on short term-storage-- at various- t@-mper-atures. A "4+" prepar@tion,has the best physical characteristics of the'materials list&d in"'ih6 tables. 'Values'of 1+''to 3 +,were assigne,d to prepaiail6ns falling in between @ t hese two extremes. Suspensions, rated 1+-Ior 2+ are not regarded- as - satisfactory for cbmniercial purpo@es. -A composite evaluation of s@mples stored @at forty degrees cefiii@r@de, 25'd'egr-ees centigrade, and four degrees ce,n-ti- grade was' m-a'de, and the rating assigned io the whole group. Pertinent remarks are included under the headi@ig "comments," It will be iioted that@ various amounts - 6f p(ly,@inyl pyrrolidone and low viscosity @odium 6arboxy- methylcelliilose wete@ u@ed. Other niaterials (e.g., -buffers, preservatives, siirface active ageiits an' d, the like) were @18o included to ddter- Wliere typ6 bf mine their'effect upon the susperi@i6n. pariі6le is iioi stated',it is to be unddtstood that a @pr' IP ec 1- tated or crystalline @toduct was UsOd@ The term "sodium CMC L.V@" r6fers to lu C YM s6d' m arbox ethylcelliii - qse having a viscosity in 2% aqueous solution of 25 to 50 centipoises At 25 d@egrees 66iitigtade. The idim "@bdiiim @,A4C@ '14 V . " r e f e r s t o @ s o c l i u m c a r b o x y m e t h y l e e l l u l o s e having a @i8cosity I in i% aqiieoui'solution 'o@f -1500('to 2200 centipoises at a . n e -'ex6ept- *hdr6-other@vise the sus@ension '4@6n- PVP is, of course, an abbreviation for polyvinyl pyr- tained O@57 petcetit sodium - citra@te an'd @O.26 'percent rolidone, while CMC is an abbreviation for sodiiini car- 75 @hethyl@orab6n. All- - @mounts are@ indicated iii perc6nt@ges,

OCR Scanned Text (5):
2,897,120 '1 0 TABLE III @@ve@n's'lo@ n hyd-row,riiso@ne @Pere.entage composition Evaluation ofisuspensions Sodium Sodium, Comments Hydro- PVP CMC Sodhi@n chlor- Preservative I Mo. 3 mo. 6mo. corti- LV citrate ide soiie 6.0 ----- 0.1 0.75 ------ 0.9 0.26 methylp@raben- 5.0----- 0.5 ------ 0.67 ----- ----- do --------- -------

5.0 ----- ------ 0.5 0.57 ----- ----- do@ --------- ------ '5 0 ----- '0.5 10.5 @0. 57 ------ ---- @.do ---------- 5:0 ----- 0.5 0.5 0@ 57 -d 0: 5.0 ----- 0.75 0.75 0.57 ----- ------ d6 --------- ------ 5.0 ----- 0.75 0.75 0. 67 ----- ------ do ---------- 6.0 --- 0:75 5;0 ----- 0 75 0.75 0.57 ----- ----- do ---------- --- - 0.@75 O@ 57 ----- ------ do ---------- ---- .10.0 ---- 0. 5 0.5 10.57 ----- 7 5'0 ----- O' 1 0.5 0.5 10.7 b.- i m@thylpa-ra-b-e-n---- 5'0 ----- 0.75 0.75 ------ 0.9 ------ dp_--@ - ---------- 5.0 ----- 0.75 0.5 0, 7 ----- do - ------ -------- -- 5.0 ----- 0.5 -O' 75 O'5 0' @7 ---- @do ---------- 5.0 ----- 0.1 0; 75 0. 5 110.7 ---- .@do ---------- 5.0 ----- O@5 10.5 ------ 0. 9 ----- do -------- ---------- 5:0 ----- 0; 5 '0@ 5 0.5 - @do 5.0 ----- 0.1 -6f tbit 0.5 ------ 0.9 0. @erosal -------- 5.0 ---- 0.1 0.3 ------ 0.9 0.18:methyl and 0.02 . :1 propylparabei3, 5.0 ----- 0.2 0.3 ------ 0. 9 ----- do --- 5.0---- 0.3 0.3 ------ 0.9 ---- @do --- 15 0 ----- @0;1 -0;4 - ------ 1@0.9 --- @-,do- :0 ----- 0.2 0.4 -- ----- ----- d6- The, following examples .@are, illi4strative @of the compositions and process;,of.the:present @invention but are not to be construed as lifiiiting. EXAMPLE 1 35 A stei-ile @tispen@ion. @6ntz@iniiig -3,00,000,'il@ts f 0came pemeillin G in - e- adh - @li@ic @elitimeiier is pre,@-ared as follows: Each cc. of the Velii@le c6nt@iiis- 40 m.g. Sodium citr@fe,- granular,'V.S.P -5.7 ---------- - Sodium carboxymethylcellulose, viscosity"25-Ito 50 ,ceniii)oises at-25' C.; arid- @'@o. @6nc ---------- 5.0 one) 5.0 Pl@sdo@e, (polyvinyl py@@,61 d" ---------- 9terile methylparabc-n, U.S.P ------ -------- 2.63 45 Water of mj ection, suffi'c'ient 'to m:;ike- u'p 1.'O -'c@ c. The sodium citrate, sodium carboxymethylcellulose and the Plasdone are mixed in sufficient water for injection and sterilized by heating ,to 120 degrees 6entigrade for r)o thirty minutes. When the vehicle has,&6oled, t-he Ste-rile methylparaben is added. The methylparabi@n is ethylene oxide or formaldehyde sterilized. The final suspension. is prepared as fbllows: Each cc. of !the suspension contains- 55 157,500 units sterile bulk procaine - penic-illin G @@ed (4% lecithin' coated) 157,500 units sterile bulk procaine penicillin G 'nileronized (1.25% lecithin') Q.s. sterile vehicle (as prepared above) 60 The sterile bulk procaine penicillin :G, milled,, (4% leci@thin coated) and the sterile bulk procaine. peiiicfflin G, micronized (1.25% lecithin coated) are:sterilized by treatinent with ethylene oxide. T@his is, done. @before. the 65 lecithin coating is applied. After the penicilhn is@eth- ylene oxide ste,- ilized, it. is handled aseptically. The sterile mffled and micronized penicillins are adde-d @utider aseptic conditions, and the sterile suspension is @passed through a colloid mill and filled aseptically into @6terile containers. 70 p- It should be noted that "micronizing" ' roduces.,par- ticle sizes of about two to ten microns, and "milling" :LThe lecithin coating is carried out as-disclosed in U.S. application Serlal Number 108,419, filed Ajigurt 31 1949. 75 +++ S g teakili@@t4O',3mos. Re@us@eliads O.K. 0.2% Fluronlc.F68. ++ -------- ----]@acking at 25 and 41. Drainage only + -------- ---- Agglomerat6d@poor' disp6fsion i)f solids. 'Drainage. poor. -------- 'S'hght6@l@@g6iigt6p@er. @+,++ Some agglomeration. +++ 40', 3 mos. k@Lmniy D@ass. T3nable to resusp6iid. +++ +++ - Drainge fair.. 'Did@ +++ +++ mag6 fdir; 4' best. +++ Do. ++++ ---- TT S494t film@of,,solids sticks to + ---- some-Ag@lomeration. -++ 'Do. 'f 41 b t +++ +++ - Drai'nage ag, . es . .++ + ,'Sli kht@66kifig:teiidehefa@ftbr 3 inbs. +++ So meagglomeration. +++ . +++ Dr @j@iage'fdir. 86iii 6@agkiorheiation. .SliRht -film of solids sticks to -walls. "0.1% 'PlLironic'F68. ++++ Sliglit fflm of solids sticks to walls. ++++ Do. ++4 -+ ----- --- ---- @Do. ------- ---- . Do. -.Do. 7- prqdpces -,particle sizes ng from forty to sixty xangi microns. Bl@@] @E @2 A sterile suspension -contaiiiijig 3,OQQQ.0.@units, of procaine penicillin G in each cubic centirneter is prepared as follows: tadli @c.'df tfie --v6hidle: 06'jitains- .,Mg. S6diuin @-,itrdtO, gtaiiular, U.S.,P ---------- 5.7 Sodiu'm cbxb6xyn@ethylteiiiii6@e, viscosity @ 25 1 to 50 cent ip6ises@ at-25"'@C. aiid 2% conc ------ ------ 7.5 Plasdo ne (polyvinyl pytiolidbnf,,) ---- .5 Sferile - mdthylpb:raben, -'U'S @p 7 ---------- Steri,le propylparabein, - U.S.P "O 2 -- -- 1.5 -- ----------Water for injection, sufficient to -make up 1.0 cc. T-he @sodium c-itrate. @sodium P@arl)-ox MethYlGelluloSe and y the Plasdo@ne 'a-'re,' 'm,'l'xe,d-.in sufficient water for injection and stpi@@ed by he@ati4g @p, 120 4egrees centigrade for th.irty minutes. VVhen -tjie vehi@le has cooled, the sierile

m.ethylparab@e,u dnd the @st@@rile p@ppylparaben'are added. T@e h@al ed as follows: '- 'preppr Each,cc. of the suspension cont@ins- 157,500 unit@@ ''gt6iiie 'biilk,,@proc'aine - gem'cilliii, G :iiiilled (4% lecithin coated,) 157,500 units sterile, bulk n@iz@d (1@.257, l@@iihin) procaine penicillin G mic-roQ.s. ' s@terile @ v@hi@@le - (as' @r'epir led above) The stenle milled and micronized pehicillins @are:added to sufficient -sterile vehicle in a sterile container and .!@ d 'Well. '@ 'T-he@ mixe suspension is passed through a colloid mM. EXAMPLE 3 @A ster-ile - sust-)ensiOn con@ai p@pg:500,000 units of"pro caine penicillin G in -each cubic @ centimter p as@fo l ows- ise repared 11.@ .?.i @ il i, ,: .." I . Eac h c6. of the vehicle c6ntams- Mg. Sodium citrate, g ' raiiiilar, U.S.P ---------- -5.7 4:liilds e, @low visco ity 2.0 Sodfu @ii car ' bicy.ih& yl@@ Pi@id o one) ----- I o.0 --------- ne ' 0 terile m thp @y ---------- 1.5 sieiil6 l@ropy ------- -------- 0.2 Water foi '-iiijt@tionl;'-iiiffi@ieni - n-lake, up 1'.0 cc.

OCR Scanned Text (6):
The soditim citrate, sodium carboxymethylcellulose and the Plasdone are mixed in sufficient water for injection and sterilized by heating to 120 degrees centigrade for thirty minutes. When the vehicle has cooled, the sterile methylparaben and sterile propylparaben are added. The final suspension is prepared as follows: Each cc. of the suspension contains- 382,500 units sterile bulk procaine penicillin G, milled (1.25% lecithin) 127,500 units sterile bulk procaine penicillin G micronized (1.25% lecithin) Q.s. sterile vehicle (as prepared above) The sterile milled and micronized penicillins are added to sufricient sterile vehicle in a sterile container and mixed well. The sterile suspension is passed through a colloid mill. EXA@MPLE 4 Following the procedure of Example 3, a suspension containing polyvinyl alcohol is prepared by substituting an equal amount of polyvinyl alcohol for polyvinyl pyrrolidone to prepare a suspension having excellent physical stability and syringeability characteristics. EXAMPLE5 Following the procedure of Example 3, a suspension of cortisone acetate is prepared by substituting 25 milligrams per cubic centimeter of cortisone acetate (precipitated or micronized) for the procaine penicillin to produce a suspension possessing excellent physical stability and good syringeability characteristics. Good suspensions of cortisone acetate can also be formed by omitting the lecithin coating. EXAMPLE 6 Following the procediire of Example 3, a suspension of hydrocortisone is prepared by substituting fifteen milligrams per cubic centimeter of- hydrocortisone (milled or precipitated) for the procaine penicillin to produce a suspension possessing excellent physical stability and good syringeability characteristics. Good suspensions of hydrocortisone can also be obtained by omitting the lecithin coating. EXAMPLB 7 Following the procedure of Example 3, a suspension of hydrocortisone acetate is prepared by substituting fifteen niifligrams per cubic centimeter of hydrocortisone acetate (milled or precipitated) for the procaine penicfllin to pro duce a suspension possessing excerent physical stability and good syringeability characteristics. Good suspensions of hydrocortisone acetate can also be obtained by omitting the lecithin coating. EXAMPLE 8 A sterile powder containing 800,000 units of procaine penicillin G and 200,000 units of sodium penicillin G can be prepared as follows: Each vial contains- 675,000 Linits sterile bulk procaine penicillin G (4% lecithin coated) 225,000 units sterile micronized crystalline procaine penicillin G 300,000 units sterile crystalline pencillin G, sodium milled 7 mg. sterile sodium citrate, granular, U.S.P. 5.6 mg. sterile sodium carboxymethylcellulose, low viscosity 5.6 mg. sterile Plasdone (polyvinyl pyrrolidone) The powders are sterilized separately by treatment with ethylene oxide and then blended in a suitable sterile blender and packaged in a sterile bottle. On addition of one cubic centimeter of sterile water a satisfactory suspension for parenteral use is obtained on shaking. 2,897,120 12 of the present invention can be prepared. Many of these are illustrated in the various tables and general descriptive matter in the present specification. Most of the specific examples are directed to parenterals. The neces- sity for good suspensions in that field is very acute. However, good suspensions are also important in other pharmaceutical preparations, such as liquid oral preparations ophthalmic preparations, sprays, lotions, and the like. These can be prepared in the vehicle of the present in- 10 vention by using conventional pharmaceutical

techniques. Likewise the specific insoluble medicinal agents included in the specific examples are illustrative only, since the vehicle of the present invention is equally effective with many other such medicinals, for example, proges- 15 terone, testosterone piropionate, estradiol monobenzoate, sulfamerazine, sulfadiazine, sulfamethazine, aluminum salts of p-a niinobenzenesuffonamides, complex aluminum salts of penicillin and p-aminoben zenesulfonamides, riboflavin, barbiturates (e.g., phenobarbital), salicylamide, 20 and the like. It is to be understood that the invention is not to be limited to the exact details of operation or exact compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and 25 the invention is therefore to be limited only by the scope of the appended claims. We claim: 1. An aqueous vehicle for insoluble medicinal agents comprisin- about 0.1 to about one percent of a low vis- 30 cosity alkaline salt of carboxymethylcellulose and about 0.1 to about three percent of a hydrophilic polyvinyl compound selected from the group consisting of polyvinyl pyrrolidone and polyvinyl- alcohol. 2. An aqueous vehicle for insoluble medicinal agents 35 comprising from about 0.1 to about one percent of low viscosity sodium carboxymethylcellulose and about 0.1 to about three percent of polyvinyl pyrrolidone. 3. An aqueous vehicle for insoluble medicinal agents comprising about 0.5 percent of low viscosity sodium 40 carboxymethylcellulose and about 0.5 percent of polyvinyl pyrrolidone. 4. A composition of matter comprising an insoluble medicinal agent and from about 0.1 to about one percent of low viscosity sodium carboxymethylcellulose and 45 about 0. 1 to about three percent of polyvinyl pyrrolidone. 5. A composition of matt--r cot- nprising procaine penicillin and from about 0.1 to about one percent ef low viscosity sodium carboxymethyleelliilose and abolit 0.1 to about three percent of polyvinyl pyrroiidone. 50 6. A composition of matter comprising an insoluble steroid and ftom about 0.1 to one percent of low viscosity sodium carboxymethylcellulose and -.bout 0.1 to three percent of- polyvinyl pyrrolidone. 7. Product of claim 6 wherein the insoltible steroid is cortisone acetate. 8. Product of claim 6 wherein the insoluble steroid is hydrocortisone. 9. Product of claim 6 wherein the insoluble steroid is hydrocortisone acetate. 60 10 ' An aqueous dispersion medium for iri-soluble medicinal agents comprisin- minor proportions of low viscosity sodium ca6oxymethylcelltilose and pglyvinyl pyrrolidone in such amolints as to maintain a viscosity between about fifteen and eiglity centipoises at 25 degrees 65 centigrade. I 1. An aqueous dispersion medilm for insoluble - nedicinal agents comprising minor proportions of low viscosity sodium carboxyjrethylcellulose and polyviiyl pyrrolidone in such ar-riounts as to maintain a viscosity 70 between about twenty and forty centipoises at 25 degrees centigrade. 12. A therapeutic composition i-n an injectable aoucous vehicle having a viscosity between about fifteen and eighty centipoises comprising low viscosity sodium Nuraerous other compositions embodying the vehicle 7.'S. rarbox inethylcellulose, polyv-lnyl pyrrolidone, a b(affer,

OCR Scanned Text (7):
13 and procaine penicillin coated at least in part with lecithin. 13. A therapeutic composition in an injectable aqueous vehicle comprising about 0.1 to one percent of low viscosity sodium carboxym ethyleellulose, aboiit 0.1 to three percent polyvinyl pyrrolidone, and pror-aine penicillin of particle sizes ranging from about two to sixty microns and coated at least in part with lecithin. 14. A therapeutic composition in an injectable aqueous vehicle to be dispensed from a silicone coated glass container, having a pH between about 5 and 7 and a viscosity between about fifteen and eighty centipoises, wbich composition comprises a preservative, a buffer, a member selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol, a low viscosity alkaline salt of carboxymethylcellulose, and from about 300,000 to 600,000 units per cubic centimeter of procaine penicillin in varying particle sizes ranging from about two to sixty microns and coated at least in part with lecithin. 15. A therapeutic r-omposition in an injectable aqueous vehicle to he dispensed from a silicone coated glass container having a pH between about 6.5 and 6.8 and a viscosity between about twenty and forty centipoises, which composition comprises a member selected fron-i the group consisting of methyl,

propyl and butyl parabens, sodium citrate, from abo@ut 0.1 to about three percent of polyvinyl pyrrolidone, between about 0.1 and about one percent of low viscosity sodium carboxymethylcellulose, and from about 300,000 to 600,000 units per cubic centimeter of procaine penicillin in varying sizes ranging from about two to sixty microns and coated at least in part with lecithin. 16. A dry romposition for the extemporaneous pre.paration of an aqueous fluid which composition compnses a low viscosity alkaline salt of =boxymethyleellulose and a member selected from the group consisting Of polyvinyl pyrrolidone and polyvinyl alcohol, in the proportions of about 0.1 to 1 to about 0.1 to 3, and an insoluble medicinal agent. 17. A dry composition for the extemporaneous preparation of an aqueous fluid which composition comprises from about 0.1 to about one part of a low viscosity alkaline salt of carboxymethylcellulose, from about 0.1 to about three parts of a member selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol, and an insoluble medicinal agent, characterized in that on shaking with about 100 parts of water an aqueous suspension having a viscosity between about fifteen and eighty centipoises at 25 degrees centigrade is produced. 18. A composition of matter complising a water-insoluble medicinal agent having approximately equivalent 2,897,120 14 portions of particles froni about two to about ten n-ticrons and particles from about forty to about sixty microns, at least a partial lecithin coating on said particles, from about 0.1 to about one percent of low viscosity sodium carboxy- methylcellulose, and from about 0.1 to about th-ree percent of a hydrophilic polyvinyl compound selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol. 19. An injectable aqueous suspension having a viscosity 10 between albout fifteen and eighty centipoises at 25 degrees centigrade and comprising a water-insoluble medicinal agent having approximately equivalent portions of particles from about two to about ten microns and particles from about forty to about sixty microns, at least a partial 15 lecithin coating on said particles, low viscosity sodium carboxymethylcellulose and a hydrophilic polyvinyl compound selected from the group consisting of polyvinyl pyrrolidone and polyvinyl alcohol. 20. An injectable aqueous suspension having a viscosity 20 of between about twenty and about forty centipoises at 25 degrees centigrade and comprising a water-insoluble medicinal agent having approximately equivalent portions of particles from about two to about ten microns and particles from about forty to about sixty microns, at least 26 a partial lecit-hin coating on said particles, from about 0. I to about one percent of low viscosity sodium carboxymethylcellulose, and from about 0.1 to about three percent of a hydrophilic polyvinyl compound selected from the group consisting of polyvinyl pyrrolidone and poly- 30 vinyl alcohol. References Cited in the file of this patent UNITED STATES PATENTS 35 2,637, 679 Gaunt --------- --------- May 5, 1953 2,650, 217 Mace k ---------- ------- Aug. 25, 1953 2,671,749 Schultz ---------- Mar. 9, 1954 2,671,750 Macek ---------- Mar. 9, 1954 -741,573 Kirchmeyer et al - ------- Apr. 10, 1956 40 2,793,156 Souler ---------- May 21, 1957 FOREIGN PATENTS 1,060,811 France ---------- Apr. 6, 1954 880,046 Germany ---------- June 18, 1953 45 OTHER REFERENCES Mantell: "Water Soluble Gums," Reinhold Pub. Co., N.Y., 1947, pp. 152- 155. Janot: "Les Penicillines h Action Prolong6e, 99 Anns. 50 Pharm., France, January 1950, pp. 46-61. Murat: "Etudes . . . pharmacodynamiques de la poly. vinylpyrrolidone," Prod. Pharma. September 1949, pp. 397-403.

Current US Original Classification (1):
424/489

Previous Doc Next Doc Go to Doc#

L22: Entry 7 of 17 File: USPT Jul 9, 2002

DOCUMENT-IDENTIFIER: US 6417167 B1
TITLE: Lyophilized compositions containing shingoglycolipid and process for preparing them

Detailed Description Paragraph Table (1):
TABLE 3 Concentration of the active component (KRN7000) Solvents 10 .mu.g/ml 100 .mu.g/ml 200 .mu.g/ml Distilled water + 1N HCl + 1N NaOH + Propylene glycol - + Macrogol 400 - + Glycerol - + Ethanol - - - 0.5% Polysorbate 20 - - - 0.5% Polysorbate 80 - + 0.5% Cremophor + 0.5% HCO 50 + 0.5% HCO 60 + 0.5% Polyoxamer 188 + Note) Judgment of solubility (by naked eye): + not dissolved (or deposited), - dissolved.

L22: Entry 9 of 17 File: USPT Sep 9, 1997

DOCUMENT-IDENTIFIER: US 5665769 A
TITLE: Pharmaceutical composition for preventing and treating retinal diseases

Detailed Description Text (11):
Such eye-drops may further contain pharmaceutically acceptable additives such as buffers (e.g., phosphate buffer, borate buffer, citrate buffer, tartrate buffer, acetate buffer, amino acids, etc.), isotonizing agents (e.g., saccharides such as sorbitol, glucose, mannitol, etc.; polyhydric alcohol such as glycerol, polyethylene glycol, propylene glycol, etc.; salts such as sodium chloride, etc), preservatives (e.g., benzalkonium chloride; benzethonium chloride; parahydroxybenzoic acid esters such as methyl parahydroxybenzoate, ethyl parahydroxybenzoate, etc.; benzyl alcohol; phenethyl alcohol; sorbic acid; sorbic acid salts; thimerosal; chlorobutanol; etc.), pH adjusting agents (e.g., hydrochloric acid, acetic acid, phosphoric acid, sodium hydroxide, etc.), thickening agents (e.g., hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose and salts thereof, etc.), chelating agents (e.g., sodium edetate, sodium citrate, condensed sodium phosphate, etc.), solubilizers (e.g., ethanol, polyoxyethylene hydrogenated castor oil, polysorbate 80, macrogol 4000, etc.).

L22: Entry 13 of 17 File: USPT Feb 22, 1977

DOCUMENT-IDENTIFIER: US 4009283 A
TITLE: Antiinflammatory and antithrombotic compositions and method of use

Brief Summary Text (20):
For topical use as an anti-inflammatory the compounds can be formulated in a pharmaceutical carrier suitable for application to affected areas of the skin, eyes or ears. Accordingly, the compositions of this invention include those pharmaceutical forms in which the medication is applied externally for contact with the area to be treated. Conventional pharmaceutical forms for this purpose include ointments, creams, lotions, solutions, suspensions, pastes, jellies, sprays and aerosols (e.g., for oral or nasal use or on the skin), drops, suppositories, powders (e.g., for use on the skin) and the like. In preparing the desired topical formulations of the novel compound of this invention, various additives, solvents, diluents and adjuvants can be utilized. These illustratively include water, surfactants (e.g., polysorbate 80 and polyoxyethylene sorbitan monostearate), emulsifiers (e.g., glyceryl monostearate-diethylaminoethyl alkyl amide phosphate, isopropyl myristate and cetyl alcohol), alcohols (e.g., ethanol and isopropanol), lower alkyl diols (e.g., 1,3-butanediol, 2,3-butanediol, 1,2-propanediol, 1,3-propanediol), glycols (e.g., propylene glycol, glycerol, sorbitol), ointment-type bases (e.g., spermaceti, Carbowaxes, beeswax, petrolatum, lanolin), higher fatty acids and alcohols (e.g., stearic acid, stearyl alcohol, cetyl alcohol, palmitic acid), liquid paraffin and vegetable oils (e.g., peanut oil, castor oil), preservatives such as sorbic acid, parabens, chlorocresol, benzalkonium chloride) and solid diluents (e.g., lactose, starch, bentonite, talc).

L23: Entry 21 of 24 File: USPT Jun 17, 1997

DOCUMENT-IDENTIFIER: US 5639738 A
** See image for Certificate of Correction **
TITLE: Treatment of basal cell carcinoma and actinic keratosis employing hyaluronic acid and NSAIDs

Brief Summary Text (11):
The Merck Index Specifies that Hyaluronic Acid has a Molecular Weight within the range pf 50,000 to 8.times.10.sup.6 depending on source, methods of preparation, and methods of determination. The Merck Publication teaches hyaluronic acid as a surgical aid (ophthalmological).

Detailed Description Text (150):
(f) no significant cellular infiltration of the vitreous and anterior chamber, no flare in the aqueous humour, no haze or flare in the vitreous, and no pathological changes to the cornea, lens, iris, retina, and choroid of the owl monkey eye when one milliliter of a 1% solution of sodium hyaluronate dissolved in physiological buffer is implanted in the vitreous replacing approximately one-half the existing liquid vitreous, said HUA being

Detailed Description Paragraph Table (13):
Formulation 9 HYANALGESE CREAM (L) 50 ml tube Quantity 3000 ml SUP- PER- FORMULA PLIER LOT AMOUNT CENT
A. Oily Phase Liquid Wax Brooks/ 450 g 15.0% DICDD Amisol Brookswax D Brooks/ 480 g 16.0% Amisol Glycerine Amisol 150 g 5.0% B. Aqueous Phase Sterile Water Baxter AW4YA8 1950 ml --% Meglumine Falk 150 g 5.0% Sodium Hyaluronate Skymart PO1 45 g 1.5% MW 207,000 Ibuprofen BDH 150 g 5.0% Suttocide A Sutton 9.0 g 0.3%

Detailed Description Paragraph Table (18):
HYANALGESE CREAM (L) X PB 022 50 ml tube Quantity 3000 ml SUP- PER- FORMULA PLIER LOT AMOUNT CENT
A. Oily Phase Liquid Wax Brooks/ 450 g 15.0% DICDD Amisol Brookswax D Brooks/ 480 g 16.0% Amisol Glycerine Amisol 150 g 5.0% B. Aqueous Phase Sterile Water Baxter AW4YA8 1950 ml --% Meglumine Falk 150 g 5.0% Sodium Hyaluronate Skymart PO1 45 g 1.5% MW 207,000 Ibuprofen BDH 150 g 5.0% Suttocide A Sutton 9.0 g 0.3%

Other Reference Publication (18):
Camber O, Edman P, Gurny R. Influence of sodium hyaluronate on the meiotic effect of pilocarpine in rabbits. Current Eye Research 1987; 6(6): 779-784.

Other Reference Publication (34):
Reim M, Teping C. Surgical procedures in the treatment of most severe eye burns. Acta Ophthalmologica 1989-Supplementum 192; 67: 47-54.

Other Reference Publication (37):
Stegman R, Miller D. Use of sodium hyaluronate in severe penetrating ocular trauma. Acta Ophthalmol. 1986; 18: 9-13.

Previous Doc Next Doc Go to Doc#

Refine Search

Search Results -

Terms	Documents
amisol and (eye or ophthal$)	24

Database:
US Pre-Grant Publication Full-Text Database
US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L23

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Friday, June 08, 2007 **Purge Queries** Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L23	amisol and (eye or ophthal$)	24	L23
L22	polysorbate same (eye or ophthal$) same (glycerol or glycerin) same ethanol	17	L22
L21	polysorbate same (eye or ophthal$)	1111	L21
L20	amisol same (eye or ophthal$)	3	L20
L19	L18 and (polyvinyl adj1 pyrrolidone)	82	L19
L18	L17 and (polyvinyl)	427	L18
L17	L8 and 424/$.ccls.	1039	L17
L16	liposome and 424/$.ccls.	23366	L16
L15	liposome and 424/.$ccls.	0	L15
L14	liposome and 424/.ccls.	0	L14
L13	L4 and 424/.$ccls.	0	L13
L12	L8 and 424/.$ccls.	0	L12

L11	L8 and 424/$ccls.	0	L11
L10	L9 and (polyvinyl adj1 acetate)	41	L10
L9	L8 and (polyvinyl adj1 alcohol)	841	L9
L8	(liposome or phospholipid or lecithin) same (eye or ophthal$)	3274	L8
L7	L6 and 424/$.ccls.	112	L7
L6	L5 and (polyvinyl adj1 pyrrolidone)	185	L6
L5	L4 and (polyvinyl adj1 acetate)	2064	L5
L4	L3 and (polyvinyl adj1 alcohol)	4198	L4
L3	(polyvinyl) same (phospholipid or lecithin)	8073	L3
L2	amisol	90	L2
L1	amisol$	136	L1

END OF SEARCH HISTORY

Mail Blog

L6: Entry 17 of 19 File: USPT Aug 11, 1998

DOCUMENT-IDENTIFIER: US 5792753 A
TITLE: Compositions comprising hyaluronic acid and prostaglandin-synthesis-inhibiting drugs

Brief Summary Text (11):
The Merck Index Specifies that Hyaluronic Acid has a Molecular Weight within the range of 50,000 to 8.times.10.sup.6 depending on source, methods of preparation, and methods of determination. The Merck Publication teaches hyaluronic acid as a surgical aid (ophthalmological).

Detailed Description Paragraph Table (14):
FORMULA SUPPLIER LOT AMOUNT PERCENT
A. Oily Phase Liquid Wax Brooks/Amisol 450 g 15.0% DICDD Brookswax D Brooks/Amisol 480 g 16.0% Glycerine Amisol 150 g 5.0% B. Aqueous Phase Sterile Water Baxter AW4YA8 1950 ml --% Meglumine Falk 150 g 5.0% Sodium Skymart PO1 45 g 1.5% Hyaluronate MW 207,000 Ibuprofen BDH 150 g 5.0% Suttocide A Sutton 9.0 g 0.3%

Detailed Description Paragraph Table (20):
FORMULA SUPPLIER LOT AMOUNT PERCENT
A. Oily Phase Liquid Wax Brooks/Amisol 450 g 15.0% DICDD Brookswax D Brooks/Amisol 480 g 16.0% Glycerine Amisol 150 g 5.0% B. Aqueous Phase Sterile Water Baxter AW4YA8 1950 ml --% Meglumine Falk 150 g 5.0% Sodium Skymart PO1 45 g 1.5% Hyaluronate MW 207,000 Ibuprofen BDH 150 g 5.0% Suttocide A Sutton 9.0 g 0.3%

Other Reference Publication (28):
Reim M. Teping C. Surgical procedures in the treatment of most severe eye burns. Acta Ophthalmologica 1989-Supplementum 192; 67:47-54.

Other Reference Publication (31):
Stegman R, Miller D. Use of sodium hyaluronate in severe penetrating ocular trauma. Acta Ophthalmol. 1986; 18: 9-13.

Other Reference Publication (50):
Arzeno G, Miller D. Effect of sodium hyaluronate on corneal wound healing. Arch Ophthalmol 1982; 100: 152.

Other Reference Publication (52):
Balazs EA, Freeman MI, et al. Hyaluronic acid and replacement of vitreous and aqueous humor. Modern Problems in Ophthalmology: Secondary Detachment of the Retina 1971; 10: 3-21.

Other Reference Publication (57):
Binkhorst CD. Advantages and disadvantages of intracamerular Na-Hyaluronate (Healon) in intraocular lens surgery. Documenta Ophthalmologica 1981; 50: 233-235.

Other Reference Publication (149):
Maguen E, Besburn AB, Macy JI. Combined use of sodium hyaluronate and tissue adhesive in penetrating deratoplasty of corneal perforations. Ophthalmic Surgery

1984 (Jan.); 15: 55-57.

Other Reference Publication (198):
Schmut O, Hofmann H. Preparation of gels from hyualuronate solutions. Graefe's Arch. Clin. Exp. Ophthalmol. 1982; 218: 311-314.

Other Reference Publication (233):
Verstraeten TC, Wilcox DK, Friberg TR, Reel C. Effects of silicone oil and hyaluronic acid on cultured human retinal pigment epithelium. Investigative Ophthalmology & Visual Science 1990; 31(9): 1761-1766.

Previous Doc Next Doc Go to Doc#

L4: Entry 21 of 23 File: USPT Dec 20, 1983

US-PAT-NO: 4421748
DOCUMENT-IDENTIFIER: US 4421748 A

TITLE: Artificial tear aid

DATE-ISSUED: December 20, 1983

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Trager; Seymour F.	Plainview	NY	11803	
Chylinski; Victoria S.	Stroud, Glos.			GB2

US-CL-CURRENT: 514/78; 514/912, 514/915

CLAIMS:

What is claimed is:

1. An artificial tear composition comprising a sterile hypotonic aqueous solution containing from about 1.0 to 20 percent weight/volume lecithin and from about 0.1 to about 20 percent by weight of a viscosity-adjusting agent selected from the group consisting of methyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol and hydroxyethyl cellulose.

2. A composition as defined by claim 1 wherein said viscosity-adjusting agent is hydroxyethyl cellulose.

3. A composition as defined by claim 1 wherein said lecithin is lecithin sulfate.

4. A composition as defined by claim 2 wherein said hydroxyethyl cellulose is present in an amount of from about 0.1 to about 2 percent weight/volume of the composition.

5. A composition as defined by claim 1 further including a sequestering agent, a preservative agent, a buffering agent and a non-ionic surfactant.

6. A composition as defined by claim 5, wherein said sequestering agent is disodium edatate, said preservative agent is sodium ethylmercurithiosalicylate, said non-ionic surfactant is a polyoxyalkylene oleic ester of sorbitol anhydride and said buffering agent is selected from sodium and potassium phosphate and mixtures thereof.

7. A composition as defined by claim 5 wherein said non-ionic surfactant is present in an amount of from about 2 to about 10 percent weight/volume, said sequestering agent is present in an amount of from about 0.5 to about 2 percent weight/volume, said preservative agent is present in an amount of from

about 0.004 to about 0.02 percent weight/volume and said buffering agent is present in an amount of from about 0.1 to about 1.0 percent weight/volume.

Previous Doc Next Doc Go to Doc#

First Hit Previous Doc Next Doc Go to Doc#

Generate Collection Print

L4: Entry 6 of 23 File: PGPB Jun 12, 2003

DOCUMENT-IDENTIFIER: US 20030108626 A1
TITLE: Method and composition for dry eye treatment

Summary of Invention Paragraph:
[0007] The usual treatment prescribed for a dry eye condition is to alleviate its symptoms by the topical application of a tear film substitute that adds a substantial volume of liquid to the anterior surface of the eye. A typical composition functioning as a tear film substitute includes soluble polymer solutions. Of prior art interest in this regard is the U.S. Pat. No. 4,421,740 to Trager which discloses an artificial tear composition formed by an aqueous hypotonic solution of lecithin, a phospholipid, and a viscosity-adjusting agent.

Previous Doc Next Doc Go to Doc#

First Hit Fwd Refs Previous Doc Next Doc Go to Doc#

Generate Collection Print

L4: Entry 14 of 23 File: USPT Nov 9, 1999

US-PAT-NO: 5981607
DOCUMENT-IDENTIFIER: US 5981607 A

TITLE: Emulsion eye drop for alleviation of dry eye related symptoms in dry eye patients and/or contact lens wearers

DATE-ISSUED: November 9, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ding; Shulin	Irvine	CA		
Olejnik; Orest	Trabuco Canyon	CA		
Reis; Brenda L.	Costa Mesa	CA		

US-CL-CURRENT: 514/785; 514/786, 514/912, 514/915, 514/941, 514/943, 514/975

CLAIMS:

What is claimed is:

1. A method for alleviation of dry eye related symptoms in dry eye patients and contact lens wearers, said method comprising topically applying to ocular tissue an emulsion of a higher fatty acid glyceride, polysorbate 80 and an emulsion stabilizing amount of Pemulen in water, said emulsion being characterized by an absence of cyclosporin.

2. The method according to claim 1 wherein the weight ratio of the higher fatty acid glyceride to the polysorbate 80 in the emulsion is between about 0.3 and about 30.

3. The method according to claim 2 wherein the higher fatty acid glyceride in the emulsion is selected from the group consisting of castor oil and corn oil.

4. The method according to claim 3 wherein castor oil is present in the emulsion in an amount of between about 0.625%, by weight, and about 5.0%, by weight, the polysorbate 80 is present in an amount of about 1.0%, by weight, the Pemulen is present in an amount of about 0.05%, by weight, and the glycerine is present in an amount of about 2.2%, by weight.

Previous Doc Next Doc Go to Doc#